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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/383,789 08/26/99 HUGHES

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HM12/1002

EXAMINER

LUKTON, D

ART UNIT

PAPER NUMBER

1653

DATE MAILED:

10/02/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.

09/383,789

Applicant(s)

Hughes

Examiner

David Lukton

Art Unit

1653



-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jul 6, 2001
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 70-121 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 70-121 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirements.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- *See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____

Pursuant to the directives of paper No. 14 (filed 7/6/01), claims 19, 23, 33, 44-69 have been cancelled, and claims 70-121 added. Claims 70-121 are pending.

Applicants' arguments filed 7/6/01 have been considered and found not persuasive.

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The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-121 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As indicated previously, applicants have shown that Val⁸-GLP-1 can be administered to the lungs, and that certain antigenic determinants of the peptide appears in serum. However, the immunoassay which applicants are endeavoring to employ to ascertain serum concentration does not establish that the intact peptide appears in serum. The antibodies will recognize fragments of the peptide; it may well not survive long enough to reach the blood intact. This matter is discussed to some degree in Deacon (*Diabetologia* **41**, 271, 1998). For example, it is stated (page 273, col 2 last paragraph) that the immunoassay measures both intact and N-terminally degraded peptide. Accordingly, the question arises

as to whether Val⁸-GLP-1 exhibits any particular physiological effect at all when administered to the lung. There is no evidence that the peptide is in fact "useful" when delivered in this way. There is no reason to expect that merely because fragments of an untested peptide can appear in serum, that a diabetic or hyperglycemic patient would derive any benefit at all from the pulmonary administration. Moreover, there is no evidence that the peptides are "protected" from DPP-IV.

In response to the foregoing, applicants have argued that there is evidence on page 33 of the specification that intact peptides are delivered to the serum of patient. However, the data there does not distinguish between intact, unhydrolyzed peptides, on the one hand, and partially hydrolyzed (e.g., 10-20% of the peptide) on the other hand. The reality is that proteases are quite abundant in lung tissue, and protease degradation is a significant problem in pulmonary administration of peptides. [See, for example, the following references that pertain to degradation of insulin: (a) Shen Z et al., "Proteolytic enzymes as a limitation for pulmonary absorption of insulin: in vitro and in vivo investigations", *International Journal of Pharmaceutics*, (1999 Dec 10) 192 (2) 115-21; (b) Fukuda et al., "Susceptibility of insulin to proteolysis in rat lung homogenate and its protection from proteolysis by various protease inhibitors", *Biological and Pharmaceutical Bulletin*, (1995 Jun) 18 (6) 891-4; (c) Yamamoto et al., "Absorption enhancement of intrapulmonary administered insulin by various absorption enhancers and protease inhibitors in rats", *Journal of Pharmacy and Pharmacology*, (1994 Jan) 46 (1) 14-8]. Moreover, on page 6, line 21, applicants have

admitted that peptides are vulnerable to proteases in the lung. See also Byron (*Journal of Aerosol Medicine* 7, 49, 1994).

This is not to say that there have been no successes in the pulmonary administration of viable peptides; rather, the point is that there have been sufficient "failures" that one can conclude that the viability of a given untested peptide is "unpredictable". Given that administration of intact, unhydrolyzed peptides to the lung is "unpredictable", one can conclude that "undue experimentation" would be required to determine which, if any, of the claimed formulations can be administered to the lung with the result that intact insulin is conveyed to the blood (*Ex parte Forman*, 230 USPQ 546, 1986).

However, if one makes the assumption that a finite quantity of the peptide survives, e.g., 0.1% of the total peptide administered to the lung, then the following claims would be enabled, assuming further that it is well known in the art that the peptides to which the claims are drawn are in fact effective to stimulate insulin secretion, to suppress glucagon secretion, to suppress hepatic glucose output and to inhibit the process of gastric emptying. It is suggested that applicants add the following claims, and point to the references which teach that the specific peptides in question exhibit the stipulated activities (in the following claims, the designation "formula I" has been created):

200. *A method of conveying a peptide of formula I to the bloodstream of a patient comprising administering to the lungs of a patient in need thereof a peptide of formula I for a time and under conditions effective to detect the presence of said peptide in the serum of the patient.*

201. *A method of stimulating insulin secretion comprising administering to the lungs of a patient afflicted with hyperglycemia a peptide of formula I for a time and under conditions effective to detect the presence of said peptide in the serum of the patient.*

202. *A method of suppressing glucagon secretion comprising administering to the lungs of a diabetic patient a peptide of formula I for a time and under conditions effective to detect the presence of said peptide in the serum of the patient.*

203. *A method of suppressing hepatic glucose output comprising administering to the lungs of a diabetic patient a peptide of formula I for a time and under conditions effective to detect the presence of said peptide in the serum of the patient.*

204. *A method of inhibiting the process of gastric emptying comprising administering to the lungs of a patient who is in need thereof a peptide of formula I for a time and under conditions effective to detect the presence of said peptide in the serum of the patient.*

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Claims 70-121 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Each of the independent claims recite the term "effective dose", thus rendering the claims indefinite as to the objective(s) of the efficacy. (It is suggested that applicants employ the language recited above in any of claims 200-204).
- The claims are indefinite as to the endpoint and process step(s). It is suggested that the claims be amended to recite that the peptides are administered to the lungs of a patient *for a time and under conditions effective to detect the presence of said peptide in the serum of the patient.*

It is applicants, not the examiner, who believe that it is a foregone conclusion that if a GLP-I peptide is administered to the lungs, and the presence of the peptide (or an antigenic determinant thereof) can be detected in the serum, benefit will inevitably accrue to the diabetic or hypoglycemic patient. Since applicants are strongly

supportive of this view, applicants should feel no reluctance in expressing their convictions in writing.

- Various claims (e.g., 81, 88 and 95) recite the phrase "less than about" or "at least about". This renders the claim indefinite. The issue here is, which term dominates, the "about", or the "less than"...? Applicants have argued that there are more than 15,000 issued patents which recite the offending term. However, the examiner is not bound by decisions made by other examiners. Moreover, deleting the terms at issue will not reduce the scope of the claimed invention at all. For example, claim 81 is dependent on claim 80; claim 80 encompasses all diameters. Accordingly, a change in the scope of claim 81 will not affect the scope of claim 80.
- Several claims, e.g., 77 and 84 recite that the GLP-I is not administered by itself, but instead is administered in combination with a carrier so as to form a "pharmaceutical composition". However, none of the independent claims suggest or require a "pharmaceutical composition". Either the scope of the independent claims should be broadened to encompass pharmaceutical compositions, or else those claims that recite pharmaceutical compositions should be written in independent form.

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The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C.

102(f) or (g) prior art under 35 U.S.C. 103.

Claims 70-121 are rejected under 35 U.S.C. §103 as being unpatentable over Drucker (USP 5846937) in view of Galloway (USP 5705483); or Smith (USP 5908830) in view of Galloway; or Knudsen (WO 98/20895) in view of Galloway; or Gelfand (EP 0,619,322) in view of Galloway; or Kirk (WO 93/18785) in view of Galloway.

As indicated previously, Smith teaches (col 9, line 14 and col 19, line 53) the use of a GLP-1 agonist which can be administered (col 11, line 58) by pulmonary means. Drucker teaches (col 8, line 50; col 9, line 31) administration of one or more GLP analogs by pulmonary means. Knudsen teaches (p. 8, line 25) administration of GLP peptides by pulmonary means. Gelfand teaches (p. 4, line 32) administration of GLP by pulmonary means. Kirk (WO 93/18785) teaches nasal administration of GLP peptides. None of these teach the specific GLP peptide to which the instant claims are drawn. Galloway ('483) teaches (col 5, line 21) that Val⁸-GLP-1 resists the proteolytic action of DPP-IV.

Applicants have begun by arguing that since Drucker provides an example of administration by a route other than to the lung, one must ignore the teachings at col 8, line 50; and col 9, line 31. However, there is no such mandate.

Applicants have also argued that while the Smith disclosure may encompass the pulmonary administration of GLP-I, the reference does not require such. However, the fact remains that the reference encompasses the pulmonary administration of GLP-I.

Applicants have also argued that Knudsen presents a "laundry list" of routes of

administration. However, there is a sentence on page 8, line 25 in which only nasal and pulmonary spray are listed. This is not a laundry list. Applicants have similarly argued that Gelfand teaches presents a "laundry list" of routes of administration. However, pulmonary administration is recited in a sentence in which no other routes of administration are recited. In addition, there are only six routes recited. Selecting from a list of six possibilities is not "picking and choosing".

Applicants have also argued that their claimed invention excludes administration by inhaling through the nose. However, out of all the claims, only one excludes inhalation through the nose. If applicants have no interest in claiming inhalation through the nose, applicants should feel no reluctance in limiting the claims to inhalation through the mouth.

Applicants have also argued that none of the references suggest administering the GLP-I peptides to a diabetic patient. However, a review of the references will show that this conclusion is not correct.

Applicants have also argued that references do not prove that intact, unhydrolyzed peptides can be administered to the bloodstream. Applicants are correct on this point. But applicants have also not shown this to be the case.

Applicants have also argued that they are the first to discover "dry powder inhalers" and nebulizers. However, a drug formulation specialist of ordinary skill is acquainted with such.

Applicants have also argued that the references do not enable one to administer the peptides

to the "deep lung alveolar epithelium". However, applicants claims do not require this.

The rejection is maintained.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

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No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton [phone number (703)308-3213].

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



DAVID LUKTON
PATENT EXAMINER
GROUP 1600